Medical and Pediatric Oncology 28:216–222 (1997)

Malignant Peripheral Nerve Sheath Tumor Arising in a "De Novo" Ganglioneuroma: A Case Report and Review of the Literature

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A case of a "de novo" ganglioneuroma showing a large area of malignant peripheral nerve sheath tumor (MPNST) is described. The tumor arose in an 11.5-year-old girl with neither stigmata nor family history of von Recklinghausen's neurofibromatosis. In addition, the patient had no previous history of a neuroblastoma or radiation therapy. This report provides new evidence that, although rare, the spontaneous development of an MPNST in a benign ganglioneuroma can occur. Immunohistochemical and electron microscopy studies supported the finding that the spindle cell component was of nerve sheath origin. **Med. Pediatr. Oncol. 28:216–222**

Key words: ganglioneuroma; neuroblastoma; malignant peripheral nerve sheath tumor; Schwann cell; child

INTRODUCTION

Ganglioneuroma is a benign tumor composed of mature ganglion cells scattered in a "neurofibromatous" stroma. Whereas the relationship between ganglioneuroma and malignant neuroectodermal tumors as neuroblastoma and ganglioneuroblastoma (GNB) is classic and well known, the occurrence of malignant nerve sheath tumor arising in a ganglioneuroma is extremely rare.

To our knowledge, excluding Enzinger and Weiss' briefly mentioned cases [1], there exist only five reported cases of a spontaneously occurring malignant nerve sheath tumor component inside a ganglioneuroma [2–6].

There are also three other previously reported cases of malignant peripheral nerve sheath tumor (MPNST) developing at sites of prior irradiation for a primitive neuroectodermal tumor [7,8]. In this report, we describe a case of a "de novo" thoracic ganglioneuroma, inside of which a large area of MPNST developed. The clinicopathologic features of the present case are discussed and compared with those previously described.

CASE REPORT

An 11.5-year-old white girl presented to our hospital in November 1993 complaining of left lower thoracic pain since August of the same year. The pain was increasing in intensity and frequency, causing her to adopt a scoliotic posture despite nonsteroidal anti- inflammatory drugs. The patient did not have stigmata or family history of von Recklinghausen's disease. She had no history suggestive of a neuroblastoma and had never received any radiation therapy. The physical examination was within normal limits. Chest radiograph detected a paravertebral mass within the posterior mediastinum (Fig. 1). Magnetic resonance imaging (MRI) demonstrated a well-defined, heterogeneous mass, occupying the left paraspinal region from the superior border of sixth to the inferior border of the tenth thoracic vertebra, measuring $8 \times 6 \times 5$ cm. This mass produced anterior and lateral displacement of the aorta. MRI showed no intraspinal extension, but the tumor was level with three intervertebral foramen, confirming the neurogenic origin of the tumor (Fig. 2). The central part of the lesion was occupied by a heterogenous area that appeared to be a necrotic zone. Laboratory tests revealed a hemoglobin level of 119 g/L and a leukocyte count of 78×10^9/L. Human immunodeficiency virus (HIV) antibody test was negative. The serum markers including ferritin, neuron-specific enolase (NSE), lactate dehydrogenase (LDH), and urinary catecholamine metabolites were repeatedly normal. Scintigraphy by metaiodobenzylguanidine (MIBG)-I^{131} was normal. A cerebral computed tomography (CT) was normal. Bone marrow aspiration and biopsy were reported as normal.

An exploratory thoracotomy was performed with a preoperative diagnosis of mature ganglioneuroma. A large mass that appeared encapsulated was found in the

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Received 13 April 1995; accepted 11 April 1996.

Fig. 1. Chest radiograph showing a soft tissue mass in the left paravertebral region separating the posterior border of ribs, without bone erosion.

region of the sympathetic chain. It was easily removed, but a remaining fragment of tumor tissue—close to an intervertebral foramen—was determined to be malignant on frozen sections.

The presence of metastases was ruled out after complete staging had been realized.

Postoperative recovery was uncomplicated. Adjuvant therapy was recommended because of the microscopic residual disease. The patient received actinomycin D (1.5 mg/m^2), ifosfamide (9 g/m^2), and vincristine (1.5 mg/m^2) per course, every 3 weeks for 6 courses, and local radiotherapy (40 Gy in 24 divided doses) according to the protocol of treatment of sarcomas of the French Society of Pediatric Oncology.

The patient is disease free 27 months after surgery.

MATERIALS AND METHODS

Resected tissue was fixed in Bouin's fixative and in 10% formalin, embedded in paraffin and stained with hematoxylin-eosin-safran.

Immunohistochemical studies were performed. A panel of monoclonal and polyclonal antibodies against the following antigens was used: S100 protein (PS100), NSE, synaptophysin, vimentin, neurofilament (NF), desmin, striated muscle actin and smooth muscle actin, epithelial membrane antigen (EMA), CD 31, and CD 34. The peroxidase-antiperoxidase technique was used with the polyclonal antibodies, and the avidin-biotin peroxidase procedure was used with monoclonal antibodies.

Electron microscopic examination was performed on glutaraldehyde-fixed tissue.

RESULTS

Macroscopic examination showed a 130-g, well-circumscribed mass, measuring 9 × 7, 5 × 5 cm. It was firm in consistency. On cut sections, it showed a homogeneous fasciculated appearance, beige-pinkish, with some grey, necrotic or hemorrhagic foci scattered in the central part of the tumor.

Microscopic examination included optic microscopy with standard stains, immunohistochemistry, and ultrastructural microscopy.

Standard stains showed the coexistence of two patterns consisting of approximately 25% benign ganglioneuroma (Fig. 3) and 75% malignant spindle-cell tumor, with transition zones between them. The ganglioneuroma component showed mature ganglion cells scattered throughout bundles of fibrillar collagen stroma containing regular Schwann-like cells. The malignant component (Fig. 4) was composed of pleiomorphic spindle cells with large, eosinophilic cytoplasms and hyperchromatic, irregular nuclei that were spindle- shaped or lobulated. Multinucleated giant tumor cells were frequent, and mitotic activity was high, up to 20 mitoses per 10 high-power fields. The stroma showed microcalcifications and giant cells of the osteoclastic type. Transition zones showed both patterns intermingled.

Immunohistochemical study showed positivity for NSE and neurofilaments in ganglion cells (Fig. 5). In the stromal fibrillar component of the benign pattern, positivity was shown for PS100, neurofilaments, and sometimes NSE. The benign fusiform cells of the stroma showed positivity for vimentin and/or PS100 and occasionally for EMA. The malignant pleomorphic spindle cells showed a strong positivity for vimentin, and few of them (less than 1%) were PS100 positive; the same percentage of other rare malignant cells were EMA positive. These cells were intermingled with a stromal fibrillar component that was NSE positive and NF positive. CD 31 was negative except for blood vessels of the stroma. CD 34 was also negative in our case, except for the blood vessels. There was no rhabdomyoblastic differentiation (actin and desmin were negative).

Ultrastructural examination was performed on the ma-

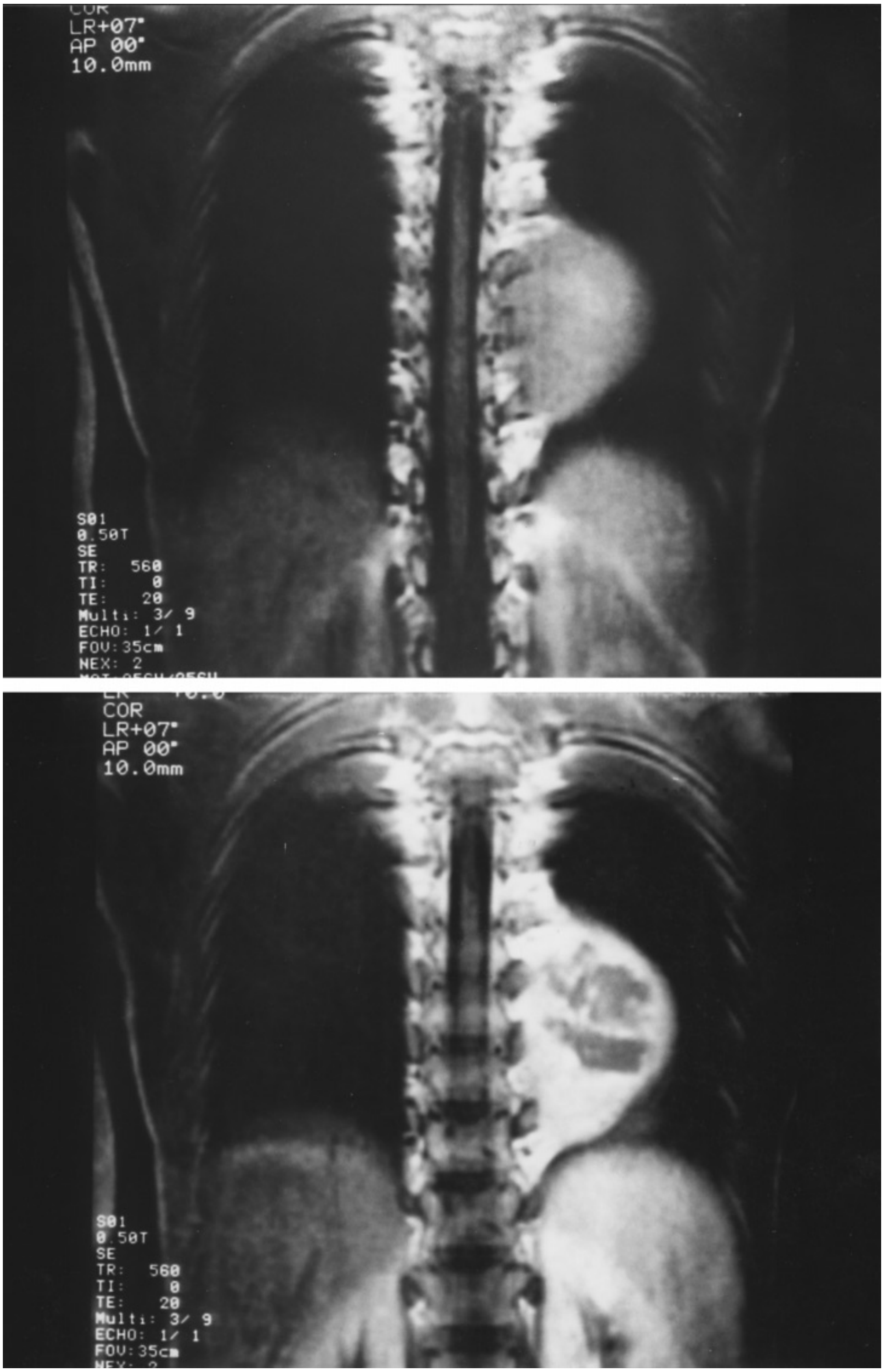

Fig. 2. Magnetic resonance imaging cuts. **(Top)** T1- weighted image (TR 560/TE 20): the mass appears isodense. **(Bottom)** T1-weighted image after gadolinium injection showing a strong and heterogeneous enhancement of the mass. No intraspinal extension.

lignant component only. The cells showed a plump cellular body with bipolar cytoplasmic expansions, not very thin and without any whorl. Micropinocytic vesicles were frequent in the elongated cytoplasmic processes, and numerous but poorly formed intercellular junctions were present, as well as focal subplasmalemmal densities. Discontinuity of the basement membrane and lack of totally continuous basement membranes were noticed, but the

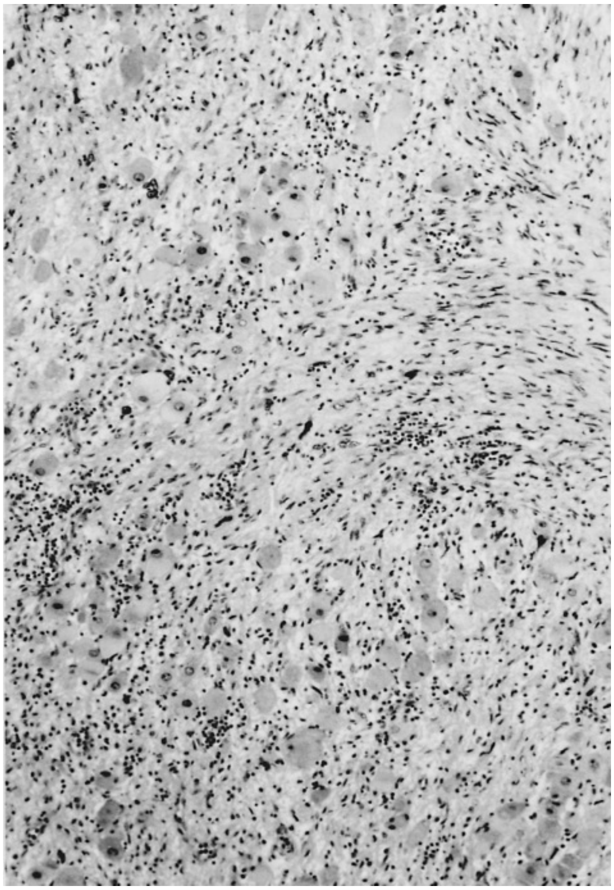

Fig. 3. Section from the region of benign ganglioneuroma showing mature ganglion cells supported by a fibrillary stroma. H&E, 100×.

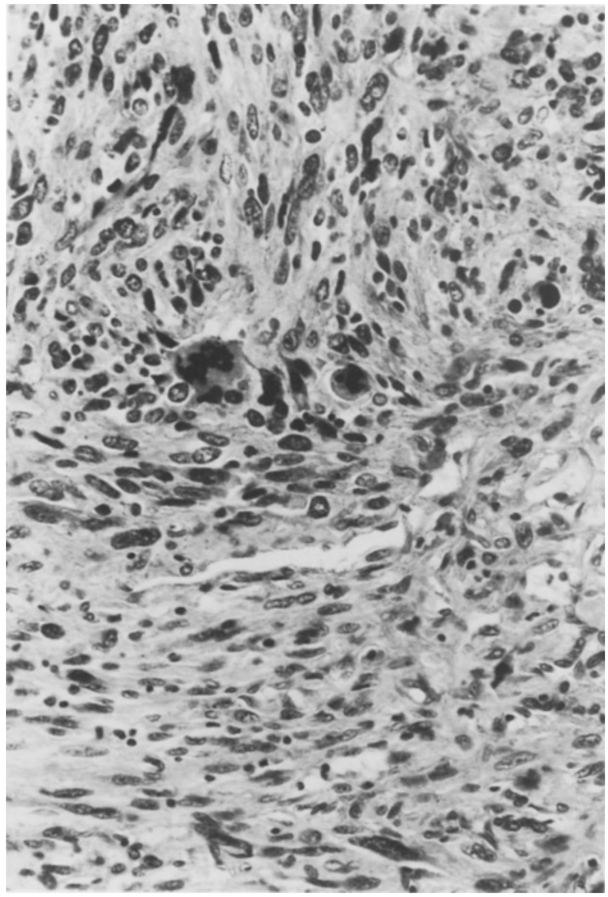

Fig. 4. Section from the area of malignant peripheral nerve sheath tumor showing high cellularity with giant nuclei. H&E, 250×.

intervals between interruptions could be long. The presence of long-spacing collagen (Fig. 7) and prominent rough endoplasmic reticulum (Fig. 6) were observed.

DISCUSSION

We describe a tumor showing features of both typical ganglioneuroma of malignant nerve sheath tumor. The light microscopic and immunohistochemical data show classical features of a benign ganglioneuroma [1]. In the malignant component, the fibrillar component stained by NSE and NF likely corresponds to neuritic expansions of the benign ganglion cells trapped inside the malignant component. The malignant component shows the characteristics of an MPNST, but neither the immunohistochemical study nor the electron microscopic study allowed any further classification. Nonetheless, this poorly differentiated population seemed to show more characteristics of a perineural cell (positivity of the EMA immunostain, micropinocytic vesicles in the elongated cytoplasmic processes, numerous intercellular junctions, focal subplasmalemmal densities, and discontinuity of the basement membrane) [9–12]. The presence of long-spacing collagen and the occasional positivity of PS100 immunostains, however, are arguments for Schwann cell differentiation [13]. Despite a prominent rough endoplasmic reticulum, which is not a classic feature of Schwann cell or perineural cell, there were no ultrastructural arguments for the fibroblastic nature of this proliferation. No areas of neuroblastoma were found in this extensively sampled tumor. This case represents a malignant nerve sheath tumor arising “de novo” from a ganglioneuroma of the thorax in childhood.

Most MPNST arise along major nerve trunks—de novo or in preexisting neurofibromas—and, in approximately half, in the setting of von Recklinghausen’s fibromatosis [1,14]. Radiation therapy can induce MPNST [15–17].

In the literature, excluding the case of Helson in 1973 (18) and the three cases reported by Enzinger and Weiss [1] (these cases being poorly documented), only eight cases of MPNST arising from ganglioneuroma, GNB, or neuroblastoma have been previously reported. Three of them arose within previously irradiated lesions (two neuroblastoma and one GNB) [7,8] after respective intervals of 17, 6, and 7 years. One arose in a “de novo” ganglioneu-

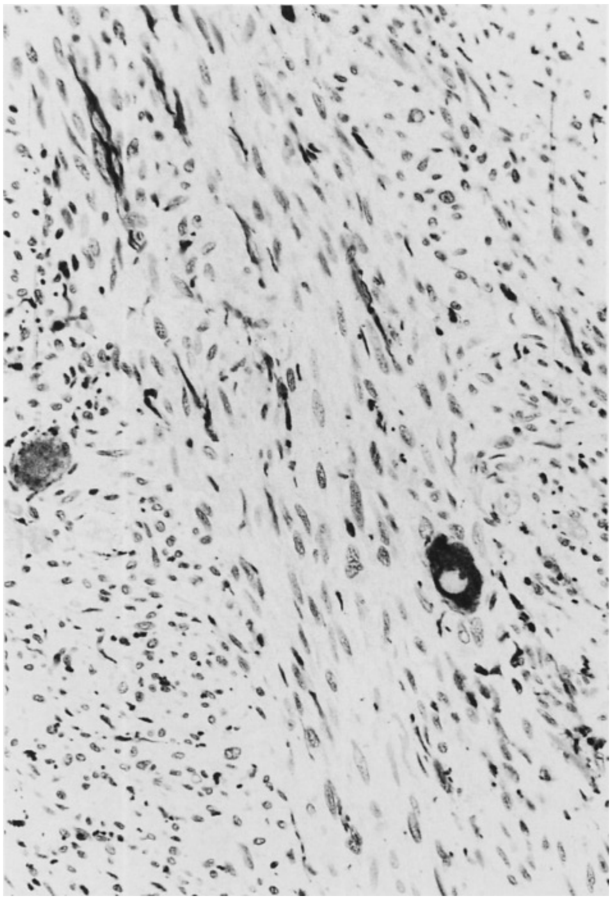

Fig. 5. Ganglion and spindle cells stained positive for neurofilament. Original magnification, 250×.

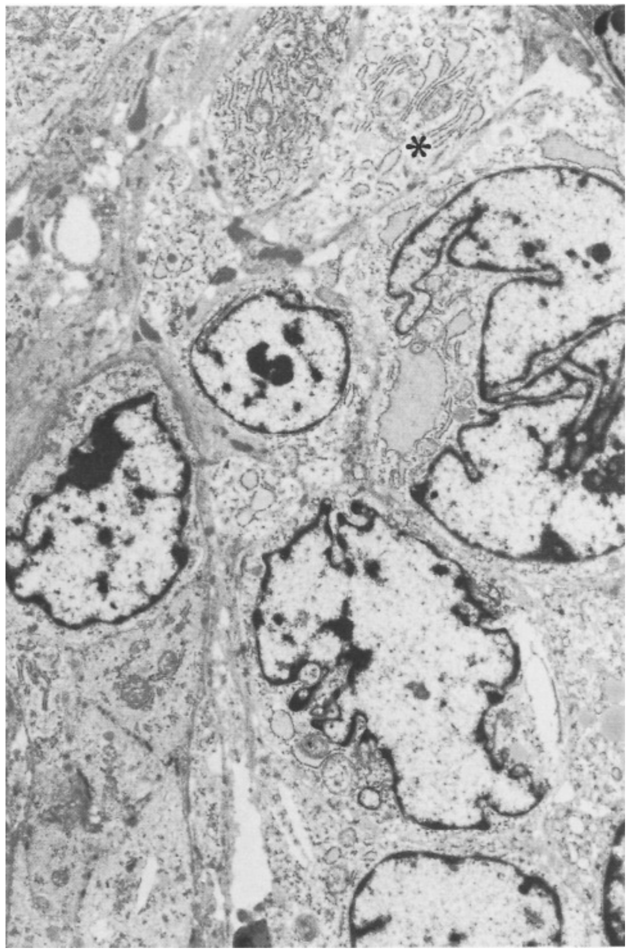

Fig. 6. Electron micrograph of the malignant component (magnification ×5800) showing pleiomorphic shape nuclei with heterochromatin condensed along the periphery of the nucleus and prominent rough endoplasmic reticulum (*).

roma in a homosexual patient, for whom the seropositivity for HIV could have been a "contributory factor" [3]. Four cases were, as in the case we describe here, the genuinely spontaneous development of an MPNST within a "de novo" ganglioneuroma (two in intra-abdominal topography, one paratesticular, and one in intrathoracic topography, as in the present case) [2,4–6].

In seven of these cases, the tumoral mass was, as in the present case, well circumscribed and showed central heterogeneous modifications. One case showed numerous abdominal nodules that were likely metastases from a primary lesion of the psoas muscle. A CT scan, performed in two cases, showed a homogeneous mass for one of the cases and a heterogeneous mass for the other. MRI, in our case showing heterogeneous central changes, was not performed in the other cases.

The evolution was a rapid relapse with metastatic dissemination in four cases. It was not mentioned in one case. The lack of recurrence after 3 years and 4 years of delay, respectively, is mentioned in two cases. Our patient shows no evidence of relapse after 27 months of evolution.

Although extremely rare, this tumor poses several interesting questions about histogenesis, the answers to which remain unclear and are debated to a large extent.

Does the ganglioneuroma "de novo" really exist, or does it always represent the evolution of a previous neuroblastoma or GNB? Although most ganglioneuromas appear totally isolated and without history of neuroblastoma in childhood, speaking against the "evolution theory", there are many arguments in favor of this theory. Such arguments include the discovery of genuine "metastatic" lesions of benign ganglioneuroma in systematic autopsies, the presence of neuroblastomatous islets in the adrenal gland or in ganglions of newborn or infant autopsies, and the coexistence of various stages of histologic maturation within the same tumor [18,19].

If the previously mentioned "evolutive" theory is true, as in at least some of the cases, does the appearance of a "Schwann-like" component inside the neuroblastoma trigger its differentiation toward GNB and ganglioneu-

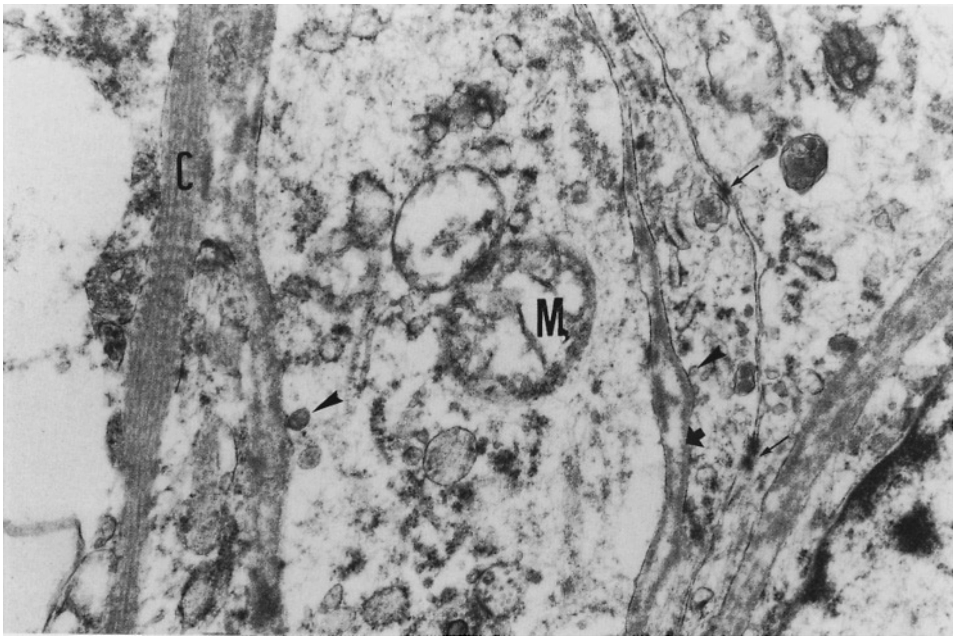

Fig. 7. Electron micrograph of the malignant component (magnification ×22100) showing mitochondria (M), pinocytic vesicles (arrow head), intercellular jonctions (thin arrow), basement membrane (thick arrow) and long spacing collagen (C).

roma? If so, how does this component appear in the neuroblastic tumor? The mechanism of the maturation of the tumor, with neuritogenesis, and development of a fibrillar stroma are poorly understood. Katsetos et al. [19] studied the controversy about the outcome of Schwann-like cells inside the neuroblastoma. Two hypotheses exist. First, the Schwann-like cell could be the result of a divergent differentiation from a neural crest stem cell constituting the early stage of the tumor. Second, the Schwann-like cell could be of stromal, non-neoplastic origin, resulting from the colonization of the tumor by blood vessels and cells from their environment. This second hypothesis poses another problem. Is the Schwann-like cell of mesenchymatous origin—as supported by the observation of a macrophagic activity—or are the blood vessels of the stroma accompanied by some nerve sheath cells originating from the neural crest?

Ambros and Ambros [20], according to ploidy studies of maturing neuroblastomas by fluorescent in situ hybridization (FISH), presented strong genetic arguments in favor of the stromal, non-neoplastic nature of the Schwann cell associated with neuroectodermal tumors. Indeed, the numerical chromosomal aberrations were restricted only to the neuronal cells (independently of their maturation level), whereas the Schwann cells showed a disomic hybridization pattern. These authors also studied the tight relationship between the neuroblastic cell (able to form axonal expansions and to promote the Schwann cell proliferation) and the Schwann cell (able to produce antiproliferative and differentiating factors active on neuroblastic cells). It seems possible that the neuroblastic cells are able to produce chemotactic molecules directed toward Schwann cells. These authors recalled the evidence that the likely neural crest origin of the Schwann cell component does not mean that the neuroblastoma-associated Schwann cell is derived from a neuroblastoma cell.

In our case, the immunohistochemistry and the ultrastructural studies of the malignant cells show patterns consistent with both perineural (occasional EMA positivity, micropinocytic vesicles, discontinuity of the basement membrane) and Schwann (occasional PS100 positivity, long-spacing collagen) cells [9,10,13]. The heterogeneity of nerve sheath tumors [9,10] has led most authors to abandon the terms “malignant schwannoma” or “neurofibrosarcoma” for the term “MPNST”. As long as the ontogenic relationship between the different cells of the nerve sheath, especially perineural cells and Schwann cells and their embryologic origin, stay poorly understood, the choice of this general term is more suitable. The origin of the perineural cell is still debated, and many studies support the idea that it could originate from three different cell types—fibroblast, Schwann cell, and arachnoid cap cell. Erlandson [21] found it conceivable that the perineural cell is, at least in certain cases, a functional variant of the Schwann cell. This author frequently observed transitional cells with ultrastructural features of both these distinct cell types in neurofibromas.

Once in the tumoral site, the non-neoplastic nerve sheath component could undergo a malignant transformation triggered by external events (such as radiation therapy), as described in several well-documented studies [7,8,15–17], or be potentially "facilitated" by certain immunologic conditions (as suggested by Chandrasoma for his HIV-positive patient [3]). However, it can be genuinely spontaneous as in the present case and four others [2,4–6].

CONCLUSION

We report the sixth case of MPNST arising spontaneously in a ganglioneuroma and recall the main histogenetic hypotheses about this kind of tumor. The immunohistochemistry and ultrastructural studies do not allow any exact classification of the peripheral nerve sheath component, which is consistent with both perineural cells and Schwann cells. Although extremely rare and of poorly understood histogenesis, the potential existence of a malignant nerve sheath tumor component inside a benign ganglioneuroma commands extensive sampling of the tumor, particularly in hemorrhagic and necrotic areas, even if the biological findings do not point toward a malignant tumor of the neuroectodermal type.

Our patient remains tumor free 27 months after tumor resection, adjuvant chemotherapy, and local radiotherapy.

ACKNOWLEDGMENTS

The authors thank Kirsten Vin-Christian, MD, University of California, San Francisco, California, for revision of the manuscript.

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